Received: 19 February 2018 | Revised: 17 June 2018 | Accepted: 12 July 2018

DOI: 10.1111/chd.12661

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Exercise testing and spirometry as predictors of mortality in congenital heart disease: Contrasting Fontan physiology with repaired tetralogy of Fallot

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Abstract

Objective: Risk prediction using cardiopulmonary exercise testing (CPET) in complex congenital heart disease tends to either focus on single diagnoses or complete cohorts. We aimed to evaluate patients with two distinct anatomies cared for at a single institution over the same time period to determine CPET variables associated with mortality.

Design: All Fontan and tetralogy of Fallot (TOF) subjects with CPET between November 1, 2002 and December 31, 2014 and subsequently died were identified (cases). Cases were matched 1:3 to controls with similar age, underlying anatomy and timing of exercise test.

Results: Of the 42 cases, 27 had a Fontan circulation and 15 with TOF. All Fontan patients had a low peak VO_2 but there was no significant difference between cases and controls (52.5 ± 14.7 v. 57.4% ± 13.5% predicted, $P = .11$). Spirometry values were significantly lower in Fontan cases than controls (eg, FVC 67.4 ± 19.1 v 77.6% ± 14.9% predicted, $P = .007$). Spirometry values were also lower in TOF cases than controls (% predicted FVC 62.8 ± 16.7 v 75 ± 14, $P = .006$). In contrast to the Fontan analysis, both %peak predicted VO_2 and VE/VCO_2 slope were worse in TOF cases than controls (50.1 ± 13.5 v. 68.5% ± 15.0% predicted VO_2, $P = .0004$; 33.9 ± 12.9 v 26.6 ± 4.4, $P = .002$). Multivariable analysis also identified different predictors of mortality among the anatomic subgroups. Spirometric data (FVC) correlated most strongly with mortality in Fontan patients while the VE/VCO_2 slope was most associated with outcome in TOF patients.

Conclusions: Variables most predictive of mortality in Fontan and TOF patients diverge but spirometry was abnormal and associated with mortality in both groups. When compared with age-matched controls, reduced FEV_1 and FVC correlated most strongly with mortality in Fontan patients while VE/VCO_2 slope correlated with mortality for TOF patients. These findings further support the importance of lung health in patients with complex congenital heart disease.

KEYWORDS

exercise testing, Fontan procedure, spirometry, tetralogy of Fallot

1 | INTRODUCTION

Over the past two decades, survival to adulthood of patients with complex congenital heart disease has improved. These patients now represent a rapidly growing subset of adults with congenital heart disease.[1] These patients are at elevated risk of premature morbidity and mortality, however. Fontan physiology in particular stands out in the published literature on account of its relatively high mortality rate.[2,3] Patients with repaired tetralogy of Fallot (TOF), who constitute one of the largest subgroups within the adult congenital heart disease population, have a better prognosis than patients who have had Fontan palliation. However, they remain at increased risk of premature mortality relative to the general population.[4] Identification of reliable predictors of mortality in these groups of patients is therefore a high priority for physicians who care for these patients. Multiple studies have shown that cardiopulmonary exercise test (CPET) variables are useful predictors of mortality risk in adults with congenital heart disease.[5,6] In Fontan patients, peak VO_2, change in peak VO_2, heart rate response to exercise, and oscillatory breathing have all been found to discriminate between patients at high and low risk for mortality.[5,7–9] Similarly, TOF studies have found a correlation between with morbidity/mortality and peak heart rate, peak oxygen uptake (VO_2) and the VE/VCO_2 slope.[10] However, most studies analyzed data from the first CPET study performed during the time period under investigation rather than the test closest to the clinical event. The analyzed CPET studies were therefore often performed several years prior to a patient's death. Moreover, in past studies that have assessed the prognostic value of CPET data in different congenital heart defects, a single group has been compared to a pooled cohort, or >5 anatomic subgroups have been pooled into one analysis.[6,11,12]

We therefore undertook this study to compare two complex anatomic subgroups which represent a high percentage of congenital heart disease. We also chose to evaluate data from the *last* CPET study prior to a patient's death. We hypothesized that this approach might identify prognostically important CPET variables that differ from those identified in past studies that have focused on data from CPETs more remote from a patient's death. We also hypothesized that the CPET variables predictive of outcome would differ by anatomic diagnosis, and that the differences might provide clinically important insights into the physiologic processes related to mortality in these different populations.

2 | METHODS

2.1 | Patient population

This was a retrospective study in which patients who had CPET at our institution between November 1, 2002 and December 31, 2014 were reviewed. Individual cohorts of tetralogy of Fallot and Fontan patients were identified. Data from patients who did not expend an adequate effort on the CPET (respiratory exchange ratio < 1.05) were excluded from the analyses. IRB approval was obtained.

2.2 | Study design

The mortality status of all patients who had CPET studies in the time interval of interest was determined from medical records. For the patients who had died (ie, the index cases), data from the last CPET prior to death, and the time interval between the exercise test and death were recorded. In addition, clinical and demographic data were extracted from clinical records concurrent with the CPET. For each index case, control subjects matched for age (±3 years) at the time of study and date of CPET (±1 year) were identified from the Fontan and TOF patients who had not died after CPET. Whenever possible, up to 3 control subjects were matched for each index case. The time interval between the corresponding CPET and the last follow-up was recorded, along with CPET, clinical, and demographic data identical to the index cases'. Clinical variables recorded included cause of death, concurrent medications, and anatomic variables (such as ventricular morphology, type of Fontan). For some of the older subjects, it was not possible to find 3 appropriate control subjects (details presented in Results section).

2.3 | CPET protocol

Spirometry was performed prior to each CPET. Patients then exercised on a cycle ergometer or a treadmill, depending upon patient and clinician preference. A ramp protocol was used for the cycle ergometer, with the ramp selected with the intention that the patient would reach peak exercise in ~10 min. Patients were encouraged to exercise until they could no longer keep up with the cycle or treadmill. Breath-by-breath expired gas analysis was performed using a CardiO2 metabolic cart system (Medical Graphics, St Paul, Minnesota). Twelve-lead electrographic monitoring was maintained throughout the study. Blood pressure and pulse oximetry were recorded every 2–3 min and at peak exercise. For the CPET data, we focused on % predicted values (rather than absolute or weight-normalized values) for VO_2, peak heart rate, and related variables, using prediction equations that account for age, sex, height, weight, and testing modality.[13] Restrictive pattern on spirometry was defined as FVC ≤80% predicted, normal or increased FEV_1/FVC.[14] Obstructive pattern was defined as FEV_1 ≤80% predicted and FEV_1/FVC ≤.8.

2.4 | Statistical analysis

For continuous variables, Student's *t* test or Wilcoxon rank-sum test was used to compare data from the index cases and control subjects depending on normality of distribution. Fisher's exact test or Chi-square was used to compare proportions for categorical data. Stepwise multivariable regression was performed to identify a model with up to 3 variables that best predicted. SAS 9.4 statistical software (SAS, Cary, North Carolina) was used for the statistical analyses.

TABLE 1 Demographic and clinical characteristic of Fontan and tetralogy of Fallot patients

	Fontan cases	Fontan controls	*P* value	TOF cases	TOF controls	*P* value
N	27	70		15	45	
Age at index CPET, y	28.9 ± 10.7	28.4 ± 11.8	.86	42.0 ± 15.2	41.5 ± 15	.91
Sex (% female)	41%	50%	.53	40%	47%	.66
BMI, kg/m^2	24.5 ± 5	23.5 ± 4.1	.3	26.3 ± 5.5	27.3 ± 5.7	.68
Age at death (years)	32.1 ± 10.5			43.6 ± 15		
Anatomy—TCPC v. APC (% with TCPC)	44%	33%	.3			
Anatomy TOF-PS v TOF-PA (% with PS)				33%	82%	.0004

Abbreviations: BMI, body mass index, CPET, cardiopulmonary exercise test, TCPC, total cavopulmonary connection, APC, atriopulmonary connection, TOF-PA, tetralogy of Fallot with pulmonary atresia, TOF-PS, tetralogy of Fallot with pulmonary stenosis.

3 | RESULTS

3.1 | Fontan patients

We identified a total of 27 patients with a Fontan circulation who had died or underwent heart transplant (index cases) after having had a CPET during the study period. The average age at the time of death was 32.1 ± 10.5 years; age at the time of last CPET was 28.9 ± 10.7 yrs. Other clinical and demographic data are provided in Table 1. Most patients died from either congestive heart failure or sudden death (see Figure 1). There was no significant difference between the groups for beta-blocker or digoxin usage. A higher percentage of cases were on diuretics than controls (67% of cases on diuretics versus 41% of controls, $P = .02$). No Fontan cases had been admitted to the hospital in the prior 3 months for congestive heart failure.

The exercise function of the index cases was significantly impaired (Table 2). Peak VO_2 averaged only 52.5% ± 14.7% predicted (18.1 ± 5.5 ml/kg/min). These patients were found to have both an inability to increase oxygen pulse (peak O_2 pulse 72.4% ± 19.0% predicted) and heart rate (peak HR 71.7% ± 15.0% predicted) to appropriate levels with exercise. Baseline spirometry was also quite abnormal. Average forced vital capacity (FVC) was 67.4% ± 19.1% predicted and volume of air exhaled in first second of forced expiration (FEV_1) averaged 67.8% ± 19.2% predicted. When categorized by spirometry pattern (obstructive, restrictive, both, indetermine or normal), there was no significant difference between the cases and controls ($P = .54$).

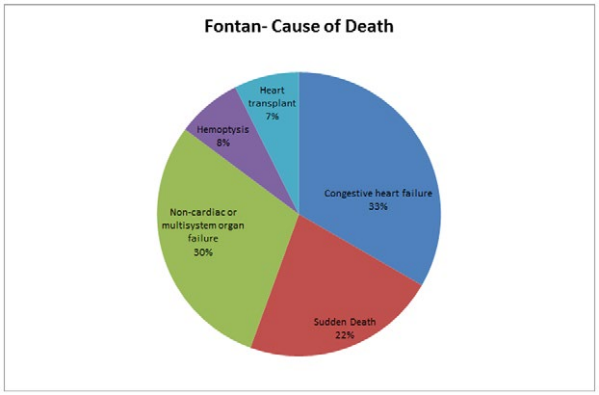

FIGURE 1 This chart demonstrates the mode of death in Fontan patients [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Fontan patients—exercise test variables

	Index cases	Control subjects	*P* value
Peak VO_2 (ml/kg/min)	18.5 ± 5.5	20.2 ± 6.2	.11
% Predicted peak VO_2	52.5 ± 14.7	57.4 ± 13.5*	.12
% Predicted FEV_1	67.8 ± 19.1	78.4 ± 13.9	.015
% Predicted FVC	67.4 ± 19.1	77.6 ± 14.9	.007
% Predicted peak O_2 pulse	72.4 ± 19	74.2 ± 16.0	.63
VE/VCO_2 slope	35 ± 10.7	33 ± 5.4*	.34
% Predicted peak heart rate	72 ± 10.5	77.9 ± 12.2	.16
Baseline O_2 sat (%)	89.6 ± 8.0*	92.2 ± 4.0*	.05
Pacemaker (% with)	44	47	.41
VO_2 at VAT	31.7 ± 8.4	34.7 ± 7.5	.1

From the database of Fontan patients with exercise tests during the period under study, it was possible to identify 3 unique control subjects conforming to criteria enumerated above for 17 of the index cases. Only 2 appropriate control subjects were found for 9 index cases and 1 index case subject had only a single appropriate control. Hence, a total of 70 control subjects were included. Their average age at the time of the CPET was 28.4 ± 11.8 yrs. They were known to have survived an average of 6.1 ± 2.7 years after the relevant CPET. Type of Fontan circulation did not correlate with outcome.

The peak VO_2 of the control subjects tended to be better than the index cases (Table 2). Their oxygen pulse and heart rate at peak

exercise also tended to be higher, although these differences did not achieve statistical significance. The most striking difference between the index and control subjects, however, was found in baseline spirometry. The control subjects' FVC averaged 77.6% ± 14.9% predicted and their FEV_1 averaged 78.4% ± 13.9% predicted. Both values were significantly superior to the index cases ($P < .02$). Statistically significant differences were not observed for any of the other clinical and demographic indices studied. A stepwise model was created and only FVC remained significantly correlated with the outcome ($P = .003$).

3.2 | Tetralogy of Fallot patients

We identified 15 patients with repaired TOF who had died (index cases) after having had a CPET in the study period. The average age at the time of death was 44.3 ± 15.3 years; age at the time of last CPET was 42 ± 15.3 yrs. Other clinical and demographic data are provided in Table 1. Sudden death occurred in 7 of the 13 patients in whom the cause of death was known (Figure 2) The cause of death was not known in 2 patients. From the database of current TOF patients with exercise tests during the period under study, it was possible to identify 3 unique control subjects conforming to criteria enumerated above for all of the index cases. Hence, a total of 45 control subjects were included in this study. Their average age at the time of the CPET was 41.6 ± 14.6 yrs. They were known to have survived an average of 5.1 ± 1.4 years after the relevant CPET. Baseline anatomy correlated with outcome as more deaths occurred among patients with a diagnosis of tetralogy of Fallot with pulmonary atresia than those who had tetralogy of Fallot with pulmonary stenosis. There was no significant difference between the groups for beta-blocker or digoxin usage. A higher percentage of cases were on diuretics than controls (64% of cases on diuretics versus 12% of controls, $P = .0001$). One TOF case was admitted with arrhythmia and heart failure in the 3 months prior to ETT.

The exercise capacity of the index cases was significantly impaired (3). Peak VO_2 averaged only 50.1% ± 13.5% predicted (15.5 ± 5.2 ml/kg/min) and was lower than controls on univariable analysis ($P = .004$). The oxygen pulse (67.5% ± 18.9% predicted) was not significantly lower in the cases. In contrast to the Fontan patients, peak heart rate and VE/VCO_2 slope were significantly lower in the cases than controls (Tables 3 and 4). Similar to Fontan patients, baseline spirometric measurements were also quite abnormal in both groups but significantly lower in the cases with average FVC of 62.8% ± 16.7% predicted and FEV_1 averaged 59% ± 15.3% predicted. When categorized by spirometry pattern (obstructive, restrictive, both, indetermine or normal), there was no significant difference between the cases and controls ($P = .06$).

On multivariable analysis, using the same approach used for Fontan patients, only VE/VCO_2 slope remained significantly correlated with the outcome ($P = .049$).

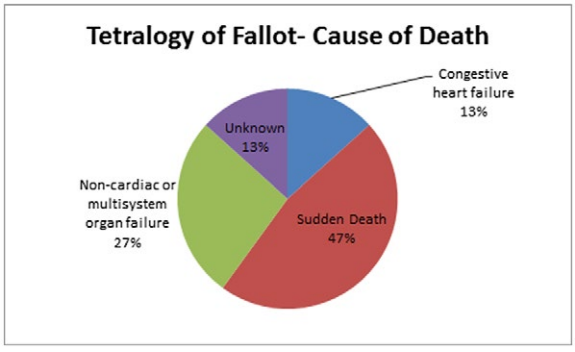

FIGURE 2 This chart demonstrates the mode of death in tetralogy of Fallot patients [Colour figure can be viewed at wileyonlinelibrary.com]

3.3 | Comparison of Fontan and TOF subjects

Comparison of the Fontan and TOF groups revealed some significant differences. Although the % predicted peak VO_2 of the Fontan and TOF index cases was similar, the % predicted peak VO_2 of the TOF control subjects was significantly higher than the Fontan control subjects. Similarly, the VE/VCO_2 slope of the TOF index cases was elevated, whereas it was in the normal range among the TOF control subjects. Among the Fontan subjects, however, the VE/VCO_2 slope was elevated in both the index cases and the control subjects. The baseline oxygen saturation of the TOF patients (both index cases and control subjects) was higher than the Fontan patients'. On multivariate analysis (Tables 5 and 6), % predicted FVC emerged as the only variable

TABLE 3 TOF patients—exercise test variables

	Index cases	Control subjects	*P* value
Peak VO_2 (ml/kg/min)	15.5 ± 5.2	21.2 ± 6.7	.004
% Predicted peak VO_2	50.1 ± 13.5	68.5 ± 15.0	.0004
% Predicted FEV_1	59.0 ± 15.3	73.3 ± 15.8	.003
% Predicted FVC	62.8 ± 16.7	75.0 ± 14.0	.006
% Predicted peak O_2 pulse	67.4 ± 18.9	77.2 ± 19.6	.10
VE/VCO_2 slope	33.9 ± 12.9	26.6 ± 4.4	.002
% predicted peak heart rate	77.0 ± 15.2	89.6 ± 12.7	.003
Baseline O_2 sat (%)	94.8 ± 5.0	97.6 ± 1.2	.09
Pacemaker (% with)	0	22	.04
VO_2 at VAT (% pred)	34 ± 9.8	41 ± 9.4	.03

Abbreviations: VO_2, oxygen consumption; FEV_1, volume of air exhaled in first second of forced expiration; FVC, forced vital capacity; *$P < .05$ vs. equivalent TOF group.

associated with mortality in the Fontan group. In contrast, only VE/VCO_2 slope was associated with mortality in the TOF group.

4 | DISCUSSION

This study focusing upon CPET data in TOF and Fontan patients prior to death is unique as we focused on CPET data from the last exercise test prior to the death of index cases and simultaneously compared them to patient groups from the same institution contemporarily. Consequently, the time interval between the CPET and the patient's demise was considerably shorter on average than that reported in prior studies examining the relationship between CPET data and mortality in patients with CHD.[5,6,12,15] This shift in focus has provided some potentially important insights into the factors associated with increased mortality risk in patients who have undergone Fontan palliation or TOF repair.

We found that, on univariable analysis, the spirometric measurements of patients who died were significantly worse than those of control subjects, both for the Fontan and the TOF subgroups. The peak VO_2, peak oxygen pulse, and peak heart rate of the survivors in the TOF subgroup were superior to those who died; however, there was no significant association between these variables and mortality in the Fontan group. The VE/VCO_2 slope was also higher in the TOF patients who died compared with survivors, whereas among the Fontan patients the VE/VCO_2 slope of those who died and those who survived was similar.

Numerous studies have detected a relationship between spirometric measurements and cardiovascular mortality. In a study of adults ≥40 years of age, the proportion of patients at high risk for cardiovascular events was twice as high among patients with FEV_1 < 80% predicted compared to those with normal FEV_1 measurements.[16] A low FVC and/or FEV_1 have also been found to be associated with increased cardiovascular mortality in other studies, and in a systematic meta-analytic review of the literature.[17–19]

Few previous studies have examined the relationship between spirometric measurements and mortality in Fontan patients. Abnormal spirometry is reported to be common among patients who have had Fontan surgery, and is independently related to reduced exercise capacity.[20] Furthermore, in a study exploring the relationship between exercise oscillatory ventilation and mortality in Fontan patients, FVC was found to be a strong univariable predictor of mortality.[8] Fernandes et al also found that the FVC and FEV_1 of Fontan patients who died tended to be lower than values encountered among Fontan

TABLE 5 Multivariable analysis—Fontan

Source	Estimate	Standard error	*P* value
BMI	−.08	.046	.071
% Predicted FVC	.13	.04	.003
VE/VCO_2 slope	−.066	.045	.14

Abbreviations as in previous Tables

TABLE 6 Multivariable analysis tetralogy of Fallot

Parameter	Estimate	Standard error	*P* value
% Predicted peak VO_2	.11	.06	.092
% Predicted FVC	.08	.05	.124
VE/VCO_2 slope	−.12	.06	.049

Abbreviations as in previous Tables

TABLE 4 Univariable analysis of predictors of mortality for each group, tetralogy of Fallot and Fontan

Variable	Tetralogy of Fallot	*P* values	Fontan	*P* values
	Correlation coefficient		Correlation coefficient	
% Predicted peak VO_2	.44	.004	.16	.11
% Predicted peak O_2 pulse	.22	.1	.05	.63
VE/VCO_2 slope	−.40	.002	−.13	.21
% Predicted FVC	.29	.007	.27	.007
% Predicted FEV_1	.32	.003	.30	.004
Peak systolic BP	.36	.027	.04	.67
Peak diastolic BP	.10	.55	.01	.92
BMI	.05	.4	−.11	.28
Baseline O_2 saturation	.40	.002	.21	.05
Breathing reserve	−.1	.68	.01	.91
% Predicted peak HR	.34	.12	.14	.16

Abbreviations: BMI, body mass index, BP, blood pressure, HR, heart rate; other abbreviations as in Table 2

patients who survived, and that a low FVC was associated with an increased risk for a combined mortality/morbidity endpoint.[7] Our findings confirm and expand upon these previous studies, and further underscore the importance of spirometric variables in patients with Fontan physiology.

Based on previous studies, we had expected to find that the peak VO_2 from the last CPET prior to a Fontan patient's death would provide highly informative prognostic information. In fact, however, peak VO_2 was not as strong a predictor of mortality as has been observed in previous studies. We believe this outcome is related to the characteristics of our study population, the timing of CPET relative to the event, and the unique features of our case-control study design. Previously published studies that found a correlation between peak VO_2 and mortality included Fontan patients who were younger and tended to have a higher peak VO_2. In contrast, we studied an emerging cohort of aging Fontan patients with more depressed peak VO_2 values. Moreover, previous studies did not always control for age and therefore did not always account for the influence of age on mortality.[5,7] In contrast, our index cases and control subjects were age-matched and the independent impact of age on mortality therefore did not confound our analyses. Finally, because our study design limited our comparisons to a relatively small number of control subjects, the ability of our study to detect a relationship between peak VO_2 and mortality was reduced compared to studies which employed other, more inclusive designs.

The mechanisms responsible for the relationship between spirometric measurements and mortality in TOF and Fontan patients remain undefined. Past investigators, when noting a correlation between spirometric abnormalities and cardiovascular risk in the general population, have speculated that abnormal spirometric measurements reflect the presence of COPD which is, at least in part, an inflammatory disease process that may affect the cardiovascular system as well as the lungs.[17–19] This explanation, initially proposed for patients with acquired heart disease, may apply to Fontan and TOF patients as well.

We believe, however, that Fontan patients' unique physiology (ie, their lack of a subpulmonary ventricle) is a more important factor underlying the observed relationship between spirometric measurements and mortality. Pulmonary blood flow in Fontan patients is "passive" and is therefore dependent upon low pulmonary vascular resistance and a healthy pulmonary vascular bed. Abnormal spirometric measurements may reflect the presence of smaller-than-normal lungs with fewer pulmonary vessels relative to body size, a condition that would be expected to have a particularly adverse effect upon the hemodynamics and health of the Fontan patient.

Similar considerations may apply to repaired TOF patients. Past morphometric studies have found that, when compared to normal subjects, patients with TOF often have fewer alveoli per terminal bronchus.[21] These microscopic abnormalities would, on a macroscopic level, be associated with small lung volumes and abnormal spirometric measurements. Moreover, since each alveolus possesses a tuft of capillaries, the morphometric studies also imply that, on a microscopic level, the pulmonary vascular bed of patients with TOF tends to be hypoplastic. The hemodynamic consequences of this pulmonary vascular hypoplasia would, in many respects, resemble the pernicious effects of PA stenoses on patients with repaired TOF. These stenoses exacerbate the regurgitation of the incompetent pulmonary valve that is almost invariably present following TOF repair, and thereby impose a pressure *and* volume overload upon the TOF patient's (often dysfunctional) RV, especially during exercise.[22,23] PA stenoses may therefore have a profound deleterious effect upon the exercise physiology/function of these patients, and probably upon their health and survival as well. In this regard, a hypoplastic pulmonary vascular bed might be expected to have similar adverse hemodynamic and clinical consequences.

The elevated VE/VCO_2 slope, and its link to mortality in patients with TOF, has been attributed to pulmonary blood flow maldistribution (and consequent ventilation/perfusion mismatch) secondary to pulmonary artery stenoses.[22,23] In contrast, the elevated VE/VCO_2 slope commonly encountered in patients with Fontan physiology is likely to a large extent due to pulmonary blood flow maldistribution secondary to the absence of a subpulmonary ventricle and the consequent abnormal, nonpulsatile pulmonary blood flow.[24,25] Since this is a condition common to all Fontan patients, the strong prognostic significance that has been associated with an elevated VE/VCO_2 slope in TOF patients is not encountered in studies of patients who have had a Fontan procedure.[5,7] Hence, our findings regarding the VE/VCO_2 slope in the Fontan and TOF subgroups conform with the results of past studies.[5,7]

The comparison of the Fontan and TOF subjects provided other informative insights. The Fontan patients were considerably younger than their TOF counterparts. This observation is consistent with the fact that the life expectancy of patients with Fontan surgery is shorter than that of patients who have undergone TOF repair.[2,4] The peak VO_2 of the Fontan survivors also tended to be lower than that of the TOF survivors, a finding consistent with the fact that the exercise function of patients with repaired TOF tends to be superior to that of Fontan patients.[26] However, in both the Fontan and TOF groups, the peak VO_2 of the patients who did not survive was similarly depressed (indeed, the peak VO_2 of the TOF patients who died was slightly lower than survivors in the Fontan group). This suggests that a patient's prognosis is poor once exercise function declines below a certain level (peak VO_2 ~50%-55% of predicted), regardless of the underlying anatomy/physiology. In populations where the average "normal" peak VO_2 is markedly depressed, as with the Fontan circulation, peak VO_2 will have less power to distinguish patients who will suffer adverse outcomes from those who do not but, somewhat paradoxically, that does not imply that the measurement has less profound implications.

5 | CONCLUSION

We found that, although the variables predictive of mortality in Fontan and TOF patients diverge, abnormal spirometry is common in both patient groups and appears to have an important association

with mortality, especially in Fontan patients. These observations suggest that interventions that preserve and/or improve pulmonary function may have an important beneficial impact upon the survival of these patients. Prospective studies should be undertaken to further explore this possibility. Among TOF patients, poor exercise capacity and ventilatory efficiency carry particularly ominous implications. Additional studies should be undertaken to determine whether measures to avert or reverse this development (eg, exercise training programs) have a beneficial impact upon mortality.

6 | LIMITATIONS

This was a retrospective study and is therefore subject to the limitations of that study design. It is also possible that CPET studies were not used uniformly for all patients; a bias related to this non-uniformity may have affected our results. However, over the past two decades, CPET has become a standard component of the evaluation and management of adolescents and adults who have had Fontan palliation or TOF repair. We therefore feel that any bias related to these factors is small. The data for this study were also derived from a single, referral institution. Consequently, our findings may not be generalizable to other settings. Finally, the power of this study was limited because the number of index cases was relatively small, due to the rarity of congenital heart disease and the low absolute mortality rates encountered in this relatively young population.

ACKNOWLEDGMENT

The authors gratefully acknowledge the expert technical assistance of Tracy J. Curran, MS, Julieann O'Neill, MS, Jennifer L. Smith, MS, and Laura E. Bourette, MS.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

AUTHOR CONTRIBUTIONS

Dr Shafer and Dr Rhodes contributed to the conception and design of the study, collection and analysis of the data, and drafting of the manuscript. Dr Opotowsky contributed to the analysis of the data and drafting of the manuscript.

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How to cite this article: Shafer KM, Opotowsky AR, Rhodes J. Exercise testing and spirometry as predictors of mortality in congenital heart disease: Contrasting Fontan physiology with repaired tetralogy of Fallot. *Congenital Heart Disease*. 2018;13:903–910. https://doi.org/10.1111/chd.12661